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EXAMINER	
DUFFY, BRADLEY	
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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,849	MA ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *13-34,39-62 and 67-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12,35-38,63-66,73 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/04, 7/14/05, 5/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

1. The election filed February 21, 2007, is acknowledged and has been entered. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has elected to prosecute the invention of the Group I, claims 1-12, 35-38, 63-66 and 73-74.

2. Claims 1-74 are pending in the application.

3. Claims 13-34, 39-62 and 67-72 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-12, 35-38, 63-66 and 73-74 are under examination.

Information Disclosure Statement

5. The references cited in the information disclosure statements filed on April 14, 2004, July 14, 2005 and May 1, 2006, have been considered.

While the international search reports and US application 09/451,353 were considered, they were crossed out as they do not conform with the information disclosure statement requirements. (see MPEP 609).

Priority

6. Acknowledgment is made of applicant's claim for foreign priority based on application filed in China on 06/06/2003 and 11/25/2003. It is noted, however, that applicant has not filed a certified copy of these Chinese applications as required by 35 U.S.C. 119(b).

Drawings

7. The drawings set forth as Figure 2 are objected to because they depict amino acid sequences, which are not identified by sequence identification numbers, either in the figure or in the brief description of drawings at page 8. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the drawings at page 8 of the specification to include sequence identification numbers, provided that the amino acid sequences presented in the figures are the same as the sequences given in the respective SEQ ID NO.

Specification

8. The disclosure is objected to because of the following informalities:

(a) The priority claim in the first paragraph of the specification needs to be updated to identify the serial number of the Chinese application filed November 23, 2003.

(b) The specification is objected to because numerous paragraphs contain underlined (blank) sections. (see for example paragraph [0022] and [0067]). Applicant is requested to clarify the purpose of these underlined sections and amend the specification to remove them, provided no prohibited new matter is introduced.

(c) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Example of such improperly demarcated trademarks appearing in the specification are Taxol® and Sephadex™ (see page 26, paragraph [0087] and page 63, paragraph [0211]).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

(d) The abstract of the disclosure is objected to because it contains a grammatical error in the first line. It appears the word "is" should be replaced with "are." Correction is required. See MPEP § 608.01(b).

(e) The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figure 2 are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 8. Furthermore it appears that at least the sequences designated KOL and REI is not in the sequence listing as filed. Finally Applicant is reminded that the sequence fragments of 4 or more amino acids given in ReSMVH and ReSMVL of Figure 2 also require reference to SEQ ID Nos. However, if these fragments occur in a larger sequence applicant can satisfy the sequence requirements by specifically enumerating the corresponding residues in the SEQ ID NO already in the sequence listing (e.g. the amino acid sequence KENF is the amino acid sequence of residues 289-293 of SEQ ID NO:431). Applicant must provide appropriate amendments to the specification or

drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

(f) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

9. Claims 6 and 12 are objected to for reciting "wherein the variable region of heavy chain". It appears the claims should properly recite "wherein the variable region of the heavy chain".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-5, 7-11, 35-38, 63-66, and 73-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-5, 7-11, 35, 37, and 63-66 are directed to a genus of antibodies, *which compete for binding to an antigen with another antibody.*

The claims are indefinite for the following reasons:

The term "competitively inhibits" is not expressly defined in the specification, so it may not be immediately clear what functional attribute characterizes the claimed antibody; moreover, as discussed in greater detail below, the degree to which the claimed antibody "competes" for binding to an antigen with any one of member of the recited genus of structurally varying monoclonal antibodies, nor the methodology used to make the determination, and the conditions under which that determination are made, are not delineated by the claims and are not ascertainable from the disclosure.

The term "competition" is defined, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The process by which the activity or presence of one substance interferes with, or suppresses, the activity of another substance with similar affinities" (Copyright © 2006 Lippincott Williams & Wilkins). Given this definition, the claims are directed to antibodies that interfere with, or suppress binding of one of the recited monoclonal antibodies to an antigen, as perhaps determined using the exemplified binding assay.

While one may know how to determine whether an antibody "competes" with one of the recited monoclonal antibodies, it is apparent that the degree to which an antibody competes with another antibody is a relative or subjective expression, and the requisite degree to which the claimed antibody competes with any of the selected monoclonal antibodies cannot be ascertained from the disclosure.

Contrary to the assertion in the specification that such a binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces

conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

George et al. (*Circulation*. 1998; **97**: 900-906), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). More particularly, George et al. describes three antibodies, which bind decidedly different, non-cross-reactive epitopes on β2GPI; yet, George et al. teaches each is able to "compete" *to some extent* with any of the others for binding to the antigen (page 903, paragraph bridging columns 1 and 2). For example, George et al. teaches monoclonal antibody ILA-4 competed with itself for binding to the antigen (% inhibition = 90 ± 11% at competitor antibody concentrations of 30 μg/ml), but George et al. discloses, despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 also "competed", albeit perhaps unsubstantially with monoclonal antibody ILA-4 for binding to the antigen (% inhibition = 9 ± 4%).

Accordingly, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al.

nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

Therefore, the claims are *not* unambiguously interpreted, as it cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the recited monoclonal antibody and an antigen. Moreover, if the claimed antibody merely inhibits binding of the recited monoclonal antibody to an antigen, it cannot be determined to what requisite extent the claimed antibody must "compete" for binding to the antigen with the recited monoclonal antibody.

Finally, the claims are directed to a plurality of structurally varying monoclonal antibodies. Pointedly, different members of this plurality of antibodies do not necessarily bind the same antigen with the same affinity or avidity as any of the other monoclonal antibodies. For example, two monoclonal antibodies comprising the complementarity determining regions of one of the disclosed monoclonal antibodies, but comprising different framework regions may have substantially different binding affinities. Presuming the concentration of the antibody is not altered, depending upon the affinity and avidity that characterizes any given antibody's ability to bind an antigen, the antibody is expected to more or less effectively "compete" with another antibody that binds the same antigen. Accordingly, the metes and bounds of the subject matter that is encompassed by the claims is expected to vary depending upon which of the recited antibodies is selected and the conditions under which the ability of the claimed antibody to compete is determined.

Summarizing these points, then, it is submitted that the metes and bounds of the subject matter encompassed by the claims vary, depending upon one's interpretation of the language of those claims, as well as upon the binding characteristics of the antibody that is selected from any of the recited pluralities of monoclonal antibodies; and while notably claims could and should be given the broadest, reasonable interpretation, the claims fail to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, as they do not delineate the claimed subject matter with the requisite degree of clarity

and particularity to permit the skilled artisan to know or determine infringing subject matter.

(b) Claims 35-38 are indefinite because these claims recite the phrase "effective amount". The metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained, where the claims recite the phrase "effective amount", yet fail to state the function that is necessarily achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

At paragraph [0063] of the published application[1], the specification defines the term "effective amount" as meaning "an amount sufficient to effect beneficial or desired results including clinical results such as shrinking the size of the tumor (in the cancer context, for example, breast or liver cancer), retardation of cancerous cell growth, decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival of individuals".

Accordingly, in this instance, the claims are indefinite because it cannot be ascertained to which beneficial or desired results the claims are directed, and it is therefore uncertain what result the effective amount of the antibody must be capable of achieving. Although the specification teaches that the effective amount might be sufficient to, for example, cause shrinkage in the size of a tumor, such a disclosure is merely exemplary and not limiting[2]. The claimed pharmaceutical composition is not necessarily administered to a subject afflicted by a tumor.

Furthermore, whereas claims 35 and 36 are directed to pharmaceutical compositions, where it would be apparent that the effective amount is administered to a subject to achieve whatever effect might be required, claims 37 and 38 are drawn to kits

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[1] U.S. Patent Application Publication No. 2005/0031617 A1.

[2] Applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

comprising an effective amount of an antibody, which is not used in any particular manner or to achieve any particular purpose or objective. Consequently, claims 37 and 38 are indefinite.

In either case, it is submitted that the expected or desired effect that is to be achieved in the practice of the claimed invention is highly subjective and would tend to vary substantially; and accordingly, the claims fail to delineate with the requisite clarity and particularity the metes and bounds of the invention, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claims 73-74 are indefinite because these claims recite the phrase "which method comprises". In this case, these claims are drawn to a product, i.e., kits for assaying for human target antigen in a sample, yet then recite "which method comprises" a) and b). There is no antecedent basis in the claim supporting the limitation "which method [...]. Therefore, the metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained because while kits might comprise instructions detailing how to perform a method one would not say that the method is part of the kit. Furthermore, while the kits might comprise antibodies and other reagents, a method would not be considered to comprise these reagents, but would set forth steps to use these reagents for some purpose.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, an of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-5, 7-11, 35, 37, 63-66 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In the instant case, the claims are directed to a genus of "antibodies" that "competitively inhibit" binding an antibody to "an SM5-1 target antigen", wherein the antibody that binds the antigen is either a human antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or a humanized antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2.

The claims are directed to a genus of antibodies that bind to a member of a genus of antigens collectively term "SM5-1 target antigens"; and more particularly the claims are directed to a genus of antibodies capable of competitively inhibiting binding of an antibody to a member of this genus of antigens. Without the antigen, it is not possible to determine whether or not an antibody competitively inhibits binding of another antibody to that antigen. It is therefore necessary that the specification describe the genus of antigens to which the claims are directed with the requisite clarity and particularity to permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of its members; yet the specification does not. The specification merely describes the genus of "SM5-1 target antigens" as inclusive of two proteins of different molecular weights, which presumably have no structural or functional similarity.

Although one could potentially identify one or more "SM5-1 target antigens" to which one of the disclosed antibodies bind, and then use that antigen to determine if another antibody is capable of inhibiting its binding, so as to determine if the other antibody is encompassed by the claims, the claims are not directed to any one particular antibody that is capable of binding to the antigen, but rather a genus of structurally disparate antibodies. Such a genus of structurally disparate antibodies is

expected to have varying binding specificities and affinities, so its members may or may not bind to the same antigens with the same affinities. For example, a recombinant derivative of the disclosed humanized antibody may not bind to the same protein as the humanized antibody, and even if it were to do so, it may not bind with the same affinity, so as to compete effectively for binding to the protein with the humanized antibody. Consequently, it is not sufficient to describe the antigen by merely describing the antibody that binds to the antigen, in order to have sufficiently described the claimed genus of antibodies that are capable of competing for binding to the antigen with the antibody.

For that matter, it is not sufficient to have described a genus of antibodies, such as that encompassed by claims 6 and 12, as having a common specificity for "SM5-1", where that antigen is not defined with clarity and particularity. Claims 6 and 12 are broadly but reasonably directed to one or another genus of antibodies that bind more than one antigen and not necessarily the same antigen. The skilled artisan could not envision, recognize or distinguish antibodies that encompassed by claim 6, for example, because, although the antibodies commonly comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 9 and a light chain variable region comprising SEQ ID NO: 10, the antibodies need not bind to the same antigen, but rather to any antigen encompassed by a genus of structurally and functionally varying antigens termed "SM5-1".

In contrast to the breadth of the claims, as will be explained in further detail in the following paragraphs, the specification only adequately describes with the requisite particularity a human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 and chimeric antibodies that contain all 6 CDRs of this antibody and that bind the same epitope as this human antibody as antibodies that would "competitively inhibit" binding to an SM5-1 target antigen ofa human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10. The specification also only adequately describes with the requisite particularity a monoclonal SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:3 and the variable light chain of SEQ

ID NO:4 and chimeric antibodies that contain all 6 CDRs of this antibody and that bind the same epitope as this monoclonal antibody (e.g., the humanized antibody that comprises SEQ ID NO:1 and SEQ ID NO:2) as antibodies that would "competitively inhibit" binding to an SM5-1 target antigen of a humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2 .

However, inasmuch as the specification fails to describe the antigens to which the disclosed antibodies bind, it similarly fails to describe the particular epitope of any one of the "SM5-1 target antigens" to which the claimed and disclosed antibodies may competitively bind.

Accordingly, because the claims are directed to a genus of antibodies that competitively inhibit the binding of either the human SM5-1 antibody or the humanized SM5-1 monoclonal antibody, but which do not necessarily comprise each of the six CDRs of the corresponding antibody, there is no disclosed correlation between any one particularly identifying structural feature shared by the members of the claimed genus and any one common particularly identifying functional feature (e.g., the ability to bind competitively compete with the respective antibodies). Consequently, the skilled artisan could not immediately envision, recognize or distinguish the members of the claimed genus of antibodies from others; and therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

To further elaborate upon the reasons that the specification inadequately describes the claimed invention to satisfy the written description requirement, it is noted that the term "epitope", as it is used in the art of immunology, is more generally used in a broader context to mean an "antigenic determinant", or site on the surface of an antigen molecule to which a single immunoglobulin molecule (e.g., antibody), Major Histocompatibility Complex (MHC) antigen, B-cell receptor, or T-cell receptor binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies, MHC antigens, B-cell receptors, and T-cell receptors of many different specificities. Stedman's Online Medical Dictionary, 27th Edition, which is available on

the Internet at http://www.stedmans.com/, for example, defines the term "epitope' as "[t]he simplest form of an antigenic determinant, on a complex antigenic molecule, which can combine with antibody or T cell receptor".

Greenspan et al. (*Nature Biotechnology*. 1999; **7**: 936-937), for example, teach that defining epitopes is not as easy as it seems. Greenspan et al. recommend that it is necessary to define an "epitope" by the structural characterization of the molecular interface between the antigen and the antibody (page 937, column 2). According to Greenspan et al., an epitope will include any and all residues that make contact with a ligand, here an MHC molecule; even contacts by residues that are energetically neutral, or even destablilizing to binding are part of the epitope. Greenspan et al. further teach that an epitope will not include any residue not contacted by the ligand (i.e., an MHC molecule), even though substitution of such a residue by another might profoundly affect binding. Furthermore, Daniel et al (Virology, 202:540-549, 1994) teach the unpredictability in identifying novel epitopes or even known epitopes in a polypeptide. Daniel et al teach analyzing the primary structure of S glycoprotein with nine prediction algorithms to identify potential epitopes of the S glycoprotein and of the fifteen potential epitopes identified by the algorithms not one novel epitope was identified (see entire document, e.g., page 547). Furthermore, the algorithms were unable to identify an already characterized epitope of the polypeptide. (e.g., page 547). Accordingly, it follows that the epitope to which any given ligand binds can only be identified empirically.

While the specification discloses that one can screen for antibodies in competition assays to antibodies that bind to the same epitope as the human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or the humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2 (see page 17), it is noted that even using such a competition binding assay, the skilled artisan cannot recognize or distinguish an antibody that binds to the same epitope as another antibody because antibodies that compete with one another for binding to the same antigen do not necessarily bind the same epitope; rather, a competing antibody may

bind a distinct, yet spatially overlapping epitope, so as to be capable of sterically hindering binding of the other antibody to its epitope.

Moreover, even antibodies that bind spatially distinct epitopes may still appear to compete with one another for binding to an antigen. For example, George et al. (*supra*), describe different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). More particularly, George et al. describe three antibodies, which bind decidedly different, non-cross-reactive epitopes on β2GPI; yet, George et al. teach each is able to "compete" *to some extent* with any of the others for binding to the antigen (page 903, paragraph bridging columns 1 and 2). For example, George et al. teach that despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 "competed" with monoclonal antibody ILA-4 for binding to the antigen, β2GPI (% inhibition = 9 ± 4%).

In addition, although the skilled artisan could potentially identify antibodies encompassed by the claims by screening for antibodies that "competitively inhibit" the binding of these antibodies, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Applicant is reminded "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that

adequately describes the genus of antibodies that competitively inhibit the binding of the human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or the humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2, because no one particular epitope to which such antibodies bind has been described. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Furthermore, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the "competitively inhibit" the binding of another antibody, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). In this case, the art discloses that the SM5-1 antibody recognizes a fibronectin variant (see Trefzer et al (b), BMC Cancer, 6(8):1-12, 2006, IDS filed 5/01/2006) to which numerous monoclonal antibodies were already described in the art (see for example Liao et al, JBC, 274(25):17876-17884, 1999), so this

functional disclosure is insufficient to distinguish infringing antibodies from non-infringing antibodies.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of antibodies, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

In summary, the specification fails to describe at least a substantial number of the claimed antibodies and furthermore fails to describe a representative number of the antibodies encompassed by the claims. Moreover, the specification does not describe a correlation between any particularly identifying (i.e., substantial) structural feature that describes the presupposed representative species, which is shared by at least most of the other members of the genus, and any one particularly identifying functional feature also shared by at least most that may be attributed to the presence of the particularly identifying structural feature. Consequently, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the claimed genus of antibodies and therefore the supporting disclosure would not

reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

14. Claims 1-5, 7-11, 35-38, 63-66 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10, a humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2 or any antibodies that comprise all 6 CDRs from these antibodies and bind to the SM5-1 antigen, and **while being enabling for making and using** these antibodies in pharmaceutical compositions wherein the antibody displays ADCC and/or CDC activity or wherein said antibody is conjugated to a toxin or radioactive isotope, and **while being enabling for making and using** any antibodies encompassed by the claims that are disclosed by the prior art, **does not reasonably provide enablement for making** an antibody that "competitively inhibits" these antibodies, or which comprise fewer than each of the six CDRs of the light and heavy chain variable regions of these antibodies, or pharmaceutical compositions comprising these antibodies that do not necessarily have the ability to cause ADCC and/or CDC or are not conjugated to a toxin or radioactive isotope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person

> skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

As explained in the written description rejection of the claims above, the claims are directed to a genus of structurally and functionally disparate antibodies, as well as a genus of antigens recognized by these antibodies, which also vary both structurally and functionally.

What has not been described with clarity and particularity necessary to satisfy the written description requirement cannot be made, and or used, without undue and/or unreasonable experimentation. As explained, the members of the genus of "SM5-1 target antigens" has not been described in a manner that would permit the artisan to immediately envision, recognize or distinguish its members from other antigens; therefore, the skilled artisan could not make at least a substantial number of the antigens to which the claims are directed. It follows then that one skilled in the art could not use the antigens to which the claims are directed to identify the claimed antibody by determining if the antibody is capable of competing for binding to the antigen with a monoclonal antibody having a structure in accordance with the claims. Moreover, without the antigen, it would also not be possible to make, and then use, derivatives of any of the particularly described antibodies because one could not know whether or

how the antibody might be used if it is not known to which antigen the antibody necessarily binds.

Where the claims are directed to antibodies that "competitively inhibit" a human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or a humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2, as the epitope to which these antibody bind has not been described, the claimed invention could not be made without first characterizing the epitope, as defined by Greenspan (*supra*), to which these antibodies bind, and then screening for antibodies that also bind this epitope. As evidenced by Greenspan the determination and characterization of the epitope to which an antibody binds is not routine or conventional and would require undue and unreasonable experimentation.

One could potentially eliminate some antibodies that bind discrete epitopes on SM5-1, which are distinct from the epitope to which these antibodies bind, because these antibodies would not compete for binding to the SM5-1 antigen. However, as noted in the above written description rejection, it is not possible to identify antibodies using such competition binding assays that bind to the *same epitope* of an antigen. This is because antibodies that bind distinct epitopes of the same antigen can act to sterically inhibit binding of others, even though each recognizes a discrete epitope of the antigen; so, a competition-binding assay thus cannot serve to identify antibodies that bind the same epitope. Again, the epitope to which any antibody binds can only be determined empirically using very complex methodology, such as crystallography, mutagenesis, and/or very sensitive binding assays, and arduous analyses of the resulting data.

Furthermore, while the skilled artisan would expect that antibodies comprising all 6 CDRs of these antibodies that bind the SM5-1 antigen would "competitively inhibit" the binding of the antibody from which the CDRs were derived, it is noted that the claims are directed to any antibody that competitively inhibits the binding and the amount of guidance, direction, and exemplification set forth in the specification would not be

sufficient to enable the skilled artisan to make at least a substantial number of these antibodies without undue and/or unreasonable experimentation.

For example, Gussow et al. (Methods in Enzymology. 1991; 203: 99-121) teach that antibodies that do not graft all six CDRs from a parent antibody would not be expected to retain the binding affinity and specificity of the parent antibody. Therefore, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, the art is still characterized by a high level of unpredictability and it would be highly unpredictable whether an antibody that does not contain the six CDRs from a parent antibody would competitively inhibit the binding of that parent antibody.

An undue amount of additional experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be practiced successfully by the skilled artisan, since, as evidenced by George et al. (*supra*) for example, the skilled artisan cannot reliably and accurately predict which antibodies will "competitively inhibit" the binding of other antibodies.

Although it may be well within the skill of the artisan to graft the six CDRs from the light and heavy chain variable regions of a human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or a humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2 into the framework of a other antibodies without substantial loss of affinity and specificity, the claims are not limited to such engineered antibodies, since they are drawn to any antibody that "competitively inhibits" these antibodies. Notably, the specification fails to teach one how to make such an antibody, which would be expected to competitively inhibit the binding of these parent antibodies unless they retained the 6 CDRs of the parent antibody.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Furthermore, where the claims are directed to antibodies in pharmaceutical compositions that are not necessarily cytotoxic it is noted that the specification only exemplifies SM5-1 antibodies that retain ADCC, CDC or are conjugated to cytotoxic

moieties as cytotoxic to tumor cells (see figures 7-10) and it is well established in the art that antibodies without these activities would not be expected to be cytotoxic. This point is supported by the teachings of Campbell et al (Blood Reviews, 17:143-152, 2003). Campbell et al. teach that the only CD20 antibodies (recognizes an antigen on B cells) that have been shown to be effective in depleting primate B cells *in vivo* are antibodies such as rituximab, tositumab and ibritumomab that comprise an IgG1 Fc region and/or are radiolabeled so that they retain ADCC, CDC activity and/or are cytotoxic to the cells they target because of their radiolabel (see entire document, e.g., page 143, right column). While the antibodies of Campbell recognize a different antigen than the SM5-1 antigen, this reference serves to illustrate that is highly unpredictable whether an antibody without ADCC and/or CDC activity or that is not conjugated to a cytotoxic moiety could be used in a pharmaceutical composition unless the antibody was shown to alter a *particular* function of its target antigen that provided some therapeutic benefit.

Notably, the instant antibodies have not been shown to alter any function of the SM5-1 antigen. Furthermore, while Trefzer et al (supra) teach that the SM5-1 antibody binds to the ED-A fibronectin variant (see entire document, e.g. page 10, left column) and therefore may be a target for immunotherapy like the ED-B fibronectin variant, Berndorff et al (Clin Cancer Research, 11(19S):1053s-7063S) teach that antibodies to the ED-B fibronectin variant are conjugated to therapeutically efficacious molecules in order to deliver these molecules to the tumor (see entire document, e.g., page 7053s-7054s, bridging paragraph). Additionally, Kipps et al. (J. Exp. Med. 1985 Jan 1; 161 (1): 1-17) teaches antibodies of identical binding affinity and specificity, but which are comprised of distinct Fc domains, either have a varying ability to mediate ADCC or lack the ability all together; see entire document (e.g., the abstract). Kipps et al. found that for the antibody tested, the murine IgG2a isotype was the most effective in directing ADCC by human effector cells, whereas the murine IgG2b directed intermediate levels of ADCC activity, but IgG1 was *inactive*; see, e.g., the abstract. Thus, it may not be merely sufficient to have described an antibody as comprising an Fc effector region, as not every Fc effector region will predictably act to mediate ADCC activity of an antibody.

Furthermore, an antibody that lacks an Fc effector region, *which will not have or retain the ADCC and/or CDC activity of another antibody having such an effector domain*, is not reasonably expected to be capable of being used pharmaceutically, *unless* the antibody is conjugated or otherwise attached to a cytotoxic agent (e.g., toxin or radioisotope), which itself would kill the cell.

Therefore, the specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies that do not comprise an Fc region capable of mediating ADCC and/or CDC or a cytotoxic moiety as being able to be used as a pharmaceutical composition. The specification does not provide sufficient guidance or direction as to how to produce such an antibody that could be used pharmaceutically without an Fc region capable of mediating ADCC and/or CDC or conjugated to a toxin or radioactive isotope and there is no working example of such an antibody.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-2, 7-9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Trefzer et al (a) (Analytical Biochemistry, 286:119-128, 2000, IDS filed 05/01/2006).

Claims 1, 2, 7 and 8 are herein drawn to an antibodies that competitively inhibit the binding of a human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or a humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2. Claim 9 is drawn to said antibody comprising the three CDRs of SEQ ID NO:1 and the three CDRs of SEQ ID NO:2. Claim 11 is drawn to said antibody comprising SEQ ID NO:3 and SEQ ID NO:4.

Trefzer et al (a) teach a mouse anti-SM5-1 monoclonal antibody that binds an antigen designated SM5-1 (see entire document, e.g., abstract and page 586, right column).

Notably, the specification teaches that SEQ ID NO:3 and SEQ ID NO:4 are the heavy and light chain variable region sequences from a mouse anti-SM5-1 monoclonal antibody and that the CDRs from this antibody were grafted into a human framework to create the humanized antibody comprising SEQ ID NO:1 and SEQ ID NO:2. Thus, the humanized antibody CDRs appear identical to the CDRs of the mouse anti-SM5-1 monoclonal antibody.

While, Trefzer et al (a) does not expressly teach that the disclosed antibody comprises the three CDRs of SEQ ID NO:1 and the three CDRs of SEQ ID NO:2 or that it comprises SEQ ID NO:3 and SEQ ID NO:4, the amino acid sequence of the antibody is an inherent property of the antibody. Therefore, absent a showing of any difference, the disclosed antibody is reasonably deemed the same as the antibody to which the claims are directed because it has the same properties of the claimed antibody and is commonly designated "SM5-1"; moreover, the reference is co-authored by the Applicants of the instant application. Therefore, the antibody of the prior art would also be reasonably considered to competitively inhibit the binding of these antibodies.

Notably, the Office lacks the resources and facilities to compare the antibody disclosed by the prior art and the claimed antibody to establish whether there are any differences. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibody is different than that taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte*

Gray, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

In summary, the antibodies of the prior art are materially and structurally indistinguishable from the instantly claimed antibodies. Therefore, absent a showing of any difference, the claimed antibodies and the antibodies disclosed by the prior art are deemed the same.

17. Claims 1-2 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Liao et al (JBC, 274(25):17876-17884, 1999), as evidenced by Trefzer et al (b) (BMC Cancer. 6(8):1-12, 2006, IDS filed 05/01/2006) and George et al (*Circulation*. 1998; 97: 900-906).

Claims 1, 2, 7 and 8 are herein drawn to an antibodies that competitively inhibit the binding of a human SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:9 and the variable light chain of SEQ ID NO:10 or a humanized SM5-1 antibody that comprises the variable heavy chain of SEQ ID NO:1 and the variable light chain of SEQ ID NO:2.

As evidenced by Trefzer et al (b) (BMC Cancer. 6(8):1-12, 2006, IDS filed 05/01/2006) the SM5-1 antigen is a fibronectin variant designated ED-A. Furthermore, as evidenced by George et al antibodies do not have to bind the same epitope on an antigen to competitively inhibit the binding of another antibody *at least to some measurable extent*.

Liao et al teach two mouse monoclonal antibodies that bind the fibronectin variant ED-A. (see entire document, e.g., abstract and Figure 2).

Therefore, the disclosed antibody is reasonably deemed to be an antibody that would competitively inhibit the instantly claimed antibodies *to some measurable extent* since the antibodies bind the same antigen, i.e., the fibronectin variant ED-A.

Notably, the Office lacks the resources and facilities to compare the antibodies disclosed by the prior art and the claimed antibody to establish whether there are any differences. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibody is different than that taught by the

prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

In summary, the antibodies of the prior art are materially and structurally indistinguishable from the instantly claimed antibodies. Therefore, absent a showing of any difference, the claimed antibodies and the antibodies disclosed by the prior art are deemed the same.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claims 1,2, 7-10, 12, 36, 38, 63, 65, 66, 73 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trefzer et al (a) (Analytical Biochemistry, 286:119-

128, 2000, IDS filed 05/01/2006), in view of Carter et al (US Patent 5,821,337, 1998).

The claims are interpreted as being drawn to humanized anti-SM5-1 antibodies comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2, compositions comprising said humanized antibody and a pharmaceutically acceptable carrier, kits comprising said humanized antibodies and instructions, conjugates comprising said antibody conjugated to a toxin or radioactive isotope and kits comprising said antibodies and a means for assessing its binding to a SM5-1 target antigen.

Trefzer et al (a) teach what is set forth in the 102(b) rejection above. While Trefzer et al teach a mouse monoclonal antibody that would inherently comprise the CDRs and other murine derived sequences present in the humanized anti-SM5-1 antibody comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2, Trefzer et al (a) do not teach humanizing monoclonal antibodies with the human heavy chain KOL sequence present in SEQ ID NO:1 or the human light chain REI sequence present in SEQ ID NO:2 or compositions comprising said humanized antibody and a pharmaceutically acceptable carrier, kits comprising said humanized antibodies and instructions, conjugates comprising said antibody conjugated to a toxin or radioactive isotope and kits comprising said antibodies and a means for assessing its binding to a SM5-1 target antigen. These deficiencies are made up for in the teachings of Carter et al.

Carter et al teach methods of humanizing murine antibodies by grafting murine heavy chain CDRs and light chain CDRs into the human heavy chain KOL sequence framework and the human light chain REI framework, respectively (see entire document, e.g, column 49 and 50). Carter et al also teach methods to identify residues in the murine sequence that would be expected to be important for antigen binding and and methods of determining which residues are important (e.g., column 2, 3 and 22). Carter et al further teach humanized antibodies in compositions comprising pharmaceutically acceptable carriers for therapeutic use (see column 47), immunoconjugates comprising said humanized antibodies conjugated to a toxin or radioactive isotope (see column 45 and 43) and a means for assessing the binding of

these humanized antibodies to antigens. While, Carter et al do not expressly teach these compositions in "kits" or with "instructions", therapeutic compositions would inherently be sold in kits with instructions. Therefore, by humanizing the mouse monoclonal antibody of Trefzer as taught by Carter one would obtain the instantly claimed humanized antibody that comprises SEQ ID NO:1 and SEQ ID NO:2 and could place said antibody in compositions with a pharmaceutically acceptable carrier, in kits comprising instructions or a means for assessing its binding or conjugate it to a radioactive isotope or toxin.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the anti-SM5-1 murine monoclonal antibody of Trefzer as taught by Carter, because Carter teach that a major limitation in using rodent antibodies clinically is an anti-globulin response directed to the rodent antibody during therapy (see column 1).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to humanize the mouse monoclonal SM5-1 antibody of Trefzer with the human antibody frameworks and methods of Carter, because Carter teaches methods that are successful for CDR grafting murine CDRs into human frameworks to create antibodies that retain antigen binding and also teach that this reduces the possibility of creating an immune response to said antibodies when used in vivo to treat human patients (e.g., column 2). Thus, there would be an advantage and a reasonable expectation of success in making in the humanized anti-SM5-1 antibody comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2 and further to place said antibody in compositions with a pharmaceutically acceptable carrier, in kits comprising instructions or a means for assessing its binding or to conjugate it to a radioactive isotope or toxin, in view of Trefzer et al and Carter et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-12, 35-38, 63-66 and 73-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 72-83, 90-93, 110-113, and 122-123 of copending Application No. 11/004659. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in these copending Applications are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are described supra.

Claims 72-83, 90-93, 110-113, and 122-123 of copending Application No. 11/004659 are drawn to humanized or human antibodies that bind to an antigen bound

by a murine antibody designated HB-12588 or a murine antibody comprising the heavy chain variable region of SEQ ID NO:3 and a light chain variable region of SEQ ID NO:4. The claims are further drawn to said antibodies in pharmaceutical compositions, kits, combinations and said antibodies conjugated to toxins or radioactive isotopes.

Notably, SEQ ID NO:3 and SEQ ID NO:4 of copending Application No. 11/004659 are identical to SEQ ID NO:3 and SEQ ID NO:4 of the instant application (see claim 11 of the instant application) and the specification in application 11/004659 discloses at page 3 that the antibody designated HB-12588 binds to the SM5-1 antigen. Furthermore, this application discloses antibodies comprising SEQ ID NO:1 and SEQ ID NO:2 and antibodies comprising SEQ ID NO:9 and SEQ ID NO:10 that both bind the SM5-1 antigen and these sequences are identical to SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:9 and SEQ ID NO:10 of the instant application. Therefore, since the antibodies of 11/004659 have sequences that are identical to the instantly claimed sequences and also bind the SM5-1 antigen they would competitively inhibit the binding of the instantly claimed antibodies and anticipate the instantly claimed humanized and human SM5-1 antibodies.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending applications anticipate the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending applications.

22. Claims 1-2, 7-9 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 09/915,746. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in these copending Applications are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant

application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are described supra.

Claims 1-18 of copending Application No. 09/915,746 are drawn to monoclonal antibodies that specifically bind the same antigen as the monoclonal antibody produced by the hybridoma HB-12588.

Notably, the specification in 09/915,746 discloses at page 4 that the antibody produced by the hybridoma HB-12588 binds the SM5-1 antigen.

Since this application has the same inventorship as the instant application and the disclosed antibody has the same properties as the instantly claimed mouse monoclonal antibody this antibody would inherently be expected to have the same sequence as the instantly claimed mouse monoclonal that comprises SEQ ID NO:3 and SEQ ID NO:4.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending applications anticipate the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending applications.

23. Claims 1-2, 7-9 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 19-22 of copending Application No. 11/146518. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in these copending Applications are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant

application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are described supra.

Claims 1 and 19-22 of copending Application No. 11/146518 are drawn to antibodies that correspond to the antibody produced by the hybridoma HB-12588.

Notably, the specification in 11/146518 discloses at page 4 that the antibody produced by the hybridoma HB-12588 binds the SM5-1 antigen.

Since this application has the same inventorship as the instant application and the disclosed antibody has the same properties as the instantly claimed mouse monoclonal antibody this antibody would inherently be expected to have the same sequence as the instantly claimed mouse monoclonal that comprises SEQ ID NO:3 and SEQ ID NO:4.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending applications anticipate the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending applications.

24. Claims 1-2, 7-11, 36 and 38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16, 17, 35, 36, 50-53, 60, 63, 64, and 65 of copending Application No. 10/723,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in these copending Applications are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are described supra.

Claims 1, 16, 17, 35, 36, 50-53, 60, 63, 64, and 65 of copending Application No. 10/723,003 are drawn to chimeric proteins comprising an Fl3 ligand linked to a p230 antibody. The claims are further drawn to pharmaceutical compositions and kits comprising said chimeric proteins and instructions or pharmaceutically acceptable carriers and wherein the antibody is humanized.

Notably, the specification in 10/723,003 discloses at page 17 that the p230 antibody binds the SM5-1 antigen and is the same monoclonal antibody disclosed in application 09/915,746.

Since this application has the same inventorship as the instant application and the p230 antibody has the same properties as the instantly claimed mouse monoclonal antibody this antibody would inherently be expected to have the same sequence as the instantly claimed mouse monoclonal that comprises SEQ ID NO:3 and SEQ ID NO:4.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending applications anticipate the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending applications.

25. Claims 1-2, 7-9, 11, 36 and 38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16, 17, 36 and 37 of copending Application No. 11/004,639. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in these copending Applications are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are described supra.

Claims 1, 16, 17, 36 and 37 of copending Application No. 11/004,639 are drawn to chimeric proteins comprising an Fl3 ligand linked to a p230 antibody. The claims are further drawn to pharmaceutical compositions and kits comprising said chimeric proteins and instructions or pharmaceutically acceptable carriers.

Notably, the specification in 11/004,639 discloses at page 21 that the p230 antibody binds the SM5-1 antigen and is the same monoclonal antibody disclosed in application 10/723,003.

Since this application has the same inventorship as the instant application and the p230 antibody has the same properties as the instantly claimed mouse monoclonal antibody this antibody would inherently be expected to have the same sequence as the instantly claimed mouse monoclonal that comprises SEQ ID NO:3 and SEQ ID NO:4.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending applications anticipate the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending applications.

26. Claims 1,2, 7-10, 12, 36, 38, 63, 65, 66, 73 and 74 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 09/915,746, in view of Carter et al (US Patent 5,821,337, 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims only differ slightly in scope.

The instant claims have been described *supra*.

Claims 1-18 of copending Application No. 09/915,746 have been described supra. The claims in copending Application No. 09/915,746 do not teach humanizing monoclonal antibodies with the human heavy chain KOL sequence present in SEQ ID NO:1 or the human light chain REI sequence present in SEQ ID NO:2 or compositions

comprising said humanized antibody and a pharmaceutically acceptable carrier, kits comprising said humanized antibodies and instructions, conjugates comprising said antibody conjugated to a toxin or radioactive isotope and kits comprising said antibodies and a means for assessing its binding to a SM5-1 target antigen. These deficiencies are made up for in the teachings of Carter et al.

Carter et al has been described *supra.*

The claims in the instant application are obvious variants of claims 1-18 of copending Application No. 09/915,746 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the anti-SM5-1 murine monoclonal antibody of 09/915,746 as taught by Carter, because Carter teach that a major limitation in using rodent antibodies clinically is an anti-globulin response direct to the rodent antibody during therapy (see column 1).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to humanize the mouse monoclonal SM5-1 antibody of 09/915,746 with the human antibody frameworks and methods of Carter, because Carter teaches methods that are successful for CDR grafting murine CDRs into human frameworks to create antibodies that retain antigen binding and also teach that this reduces the possibility of creating an immune response to said antibodies when used in vivo to treat human patients (e.g., column 2). Thus, there would be an advantage and a reasonable expectation of success in making in the humanized anti-SM5-1 antibody comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2 and further to place said antibody in compositions with a pharmaceutically acceptable carrier, in kits comprising instructions or a means for assessing its binding or to conjugate it to a radioactive isotope or toxin, in view of Carter et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

27. Claims 1,2, 7-10, 12, 36, 38, 63, 65, 66, 73 and 74 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 19-22 of copending Application No. 11/146518, in view of Carter et al (US Patent 5,821,337, 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims only differ slightly in scope.

The instant claims have been described *supra*.

Claims 1 and 19-22 of copending Application No. 11/146518 have been described supra. The claims in copending Application No. 11/146518 do not teach humanizing monoclonal antibodies with the human heavy chain KOL sequence present in SEQ ID NO:1 or the human light chain REI sequence present in SEQ ID NO:2 or compositions comprising said humanized antibody and a pharmaceutically acceptable carrier, kits comprising said humanized antibodies and instructions, conjugates comprising said antibody conjugated to a toxin or radioactive isotope and kits comprising said antibodies and a means for assessing its binding to a SM5-1 target antigen. These deficiencies are made up for in the teachings of Carter et al.

Carter et al has been described *supra.*

The claims in the instant application are obvious variants of claims 1 and 19-22 of copending Application No. 11/146518 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the anti-SM5-1 murine monoclonal antibody of 11/146518 as taught by Carter, because Carter teach that a major limitation in using rodent antibodies clinically is an anti-globulin response directed to the rodent antibody during therapy (see column 1).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to humanize the mouse monoclonal SM5-1 antibody of 11/146518 with the human antibody frameworks and methods of Carter, because Carter teaches methods that are successful for CDR grafting murine CDRs into human frameworks to create antibodies that retain antigen binding and also teach that this reduces the possibility of creating an immune response to said antibodies when used in vivo to treat human patients (e.g., column 2). Thus,

there would be an advantage and a reasonable expectation of success in making in the humanized anti-SM5-1 antibody comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2 and further to place said antibody in compositions with a pharmaceutically acceptable carrier, in kits comprising instructions or a means for assessing its binding or to conjugate it to a radioactive isotope or toxin, in view of Carter et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

28. Claims 1-2, 7-8, 12, 63, 65, 66, 73 and 74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16, 17, 35, 36, 50-53, 60, 63, 64, and 65 of copending Application No. 10/723,003, in view of Carter et al (US Patent 5,821,337, 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims only differ slightly in scope.

The instant claims have been described *supra*.

Claims 1, 16, 17, 35, 36, 50-53, 60, 63, 64, and 65 of copending Application No. 10/723,003 have been described *supra*. The claims in copending Application No. 10/723,003 do not teach the human heavy chain KOL sequence present in SEQ ID NO:1 or the human light chain REI sequence present in SEQ ID NO:2 or conjugates comprising said antibody conjugated to a toxin or radioactive isotope and kits comprising said antibodies and a means for assessing its binding to a SM5-1 target antigen. These deficiencies are made up for in the teachings of Carter et al.

Carter et al has been described *supra.*

The claims in the instant application are obvious variants of claims 1, 16, 17, 35, 36, 50-53, 60, 63, 64, and 65 of copending Application No. 10/723,003 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the

claimed invention was made to humanize the anti-SM5-1 monoclonal antibody of 10/723,003 as taught by Carter, because Carter teach that a major limitation in using rodent antibodies clinically is an anti-globulin response directed to the rodent antibody during therapy (see column 1).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to humanize the mouse monoclonal SM5-1 antibody of 10/723,003 with the human antibody frameworks and methods of Carter, because Carter teaches methods that are successful for CDR grafting murine CDRs into human frameworks to create antibodies that retain antigen binding and also teach that this reduces the possibility of creating an immune response to said antibodies when used in vivo to treat human patients (e.g., column 2). Thus, there would be an advantage and a reasonable expectation of success in making in the humanized anti-SM5-1 antibody comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2 and further to place said antibody in kits comprising a means for assessing its binding or to conjugate it to a radioactive isotope or toxin, in view of Carter et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

29. Claims 11-2, 7-8, 10, 12, 63, 65, 66, 73 and 74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16, 17, 36 and 37 of copending Application No. 11/004,639, in view of Carter et al (US Patent 5,821,337, 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims only differ slightly in scope.

The instant claims have been described *supra*.

Claims 1, 16, 17, 36 and 37 of copending Application No. 11/004,639 have been described *supra*. The claims in copending Application No. 11/004,639 do not teach

humanizing monoclonal antibodies with the human heavy chain KOL sequence present in SEQ ID NO:1 or the human light chain REI sequence present in SEQ ID NO:2 or conjugates comprising said antibody conjugated to a toxin or radioactive isotope and kits comprising said antibodies and a means for assessing its binding to a SM5-1 target antigen. These deficiencies are made up for in the teachings of Carter et al.

Carter et al has been described *supra.*

The claims in the instant application are obvious variants of claims 1, 16, 17, 36 and 37 of copending Application No. 11/004,639 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the anti-SM5-1 monoclonal antibody of 11/004,639 as taught by Carter, because Carter teach that a major limitation in using rodent antibodies clinically is an anti-globulin response directed to the rodent antibody during therapy (see column 1).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to humanize the mouse monoclonal SM5-1 antibody of 11/004,639 with the human antibody frameworks and methods of Carter, because Carter teaches methods that are successful for CDR grafting murine CDRs into human frameworks to create antibodies that retain antigen binding and also teach that this reduces the possibility of creating an immune response to said antibodies when used in vivo to treat human patients (e.g., column 2). Thus, there would be an advantage and a reasonable expectation of success in making in the humanized anti-SM5-1 antibody comprising the variable heavy chain of SEQ ID NO: 1 and the variable light chain of SEQ ID NO:2 and further to place said antibody in kits comprising a means for assessing its binding or to conjugate it to a radioactive isotope or toxin, in view of Carter et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

bd
April 27, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/722,849	Applicant(s) MA ET AL.	
	Examiner Brad Duffy	Art Unit 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.

☐ 7. Other: It appears that at least the sequences designated KOL and REI in Figure 2 are not in the sequence listing as filed.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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